PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 12.08.2004
Applicant's or agent's file reference MXG/P33126	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/11423	14.10.2003	16.10.2002

Applicant
GLAXO GROUP LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MXG/P33126	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11423	International filing date *(day/month/year)* 14.10.2003	Priority date *(day/month/year)* 16.10.2002
International Patent Classification (IPC) or both national classification and IPC C07D295/18		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.05.2004	12.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11423

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-132 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 2 (part), 7

   because:

   ☒ the said international application, or the said claims Nos. 7 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 2 (part) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1,3-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1,3-6,8
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) piperazine and diazepine derivatives (I) (claims 1-2),
(ii) a pharmaceutical composition comprising compounds (I) (claim 3),
(iii) the medical use of compounds (I) (claims 4-6),
(iv) the corresponding therapeutic method (claim 7), and
(v) the medical use of the pharmaceutical composition (claim 8).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2 In view of the objections raised under item V.5.2 below a complete examination of claim 2 with regard to novelty and inventive step is at present not applicable.

Re Item IV

Lack of unity of invention

See item V.3.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 02/12214 A, 14.02.2002; cited in the application.
D2: WO 02/06223 A, 24.01.2002.
D3: WO 02/12190 A, 14.02.2002.
D4: WO 02/076925, 03.10.2002.
D5: WO 03/059341 A, 24.07.2003; & US 2002/0137931 A1, 26.09.2002.

D6: WO 03/066604 A, 14.08.2003.

Documents **D5** and **D6** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

2 Novelty

2.1 In view of **D1** to **D4** the application does not comply with the criterion of novelty according to Article 33(2) PCT.

D1 discloses histamine-3 receptor ligands, the corresponding pharmaceutical composition, and corresponding therapeutic methods. The compounds of D1 substantially overlap with the present compounds (I) when R^1 is C_{1-6}alkyl, C_{1-6} alkoxy, C_{3-7} cycloalkyl, C_{1-6}alkyl-C_{3-7}cycloalkyl, C_{1-6}alkyl-C_{2-15}heterocyclyl, C_{1-6}alkyl-phenyl; Z is a bond or CO; m = 0-2; and R^3 is $-(CH_2)_{2-4}NR^{11}R^{12}$ (cf. D1, claim 1). In addition, the document discloses already specific example within the overlapping range, of which some are excluded from present claim 1 by means of provisos (i.e. examples 24, 26, 27, 53, 88, 90, 91) but others are still within the scope of the claim (cf. examples 7 and 8 (according to present formula (I) wherein R^1 = O-i-Pr; Z = CO; m = n = r = 0; p = 1; R^3 = $-(CH_2)_3$-N-pyrrolidine respectively $-(CH_2)_3$-N-piperidine)). The present claims 1 and 3-8 lack thus novelty in view of D1. In this context it is noted that the provisos in present claim 1 are not suited to establish novelty over D1, because the teaching of this document is not merely limited to the specific examples. In order to render the present application novel vis-à-vis D1 the whole overlapping range has to be removed from present claim 1.

D2 relates to histamine-3 receptor ligands, the corresponding pharmaceutical composition, and corresponding therapeutic methods. The compounds of D2 overlap with the present compounds (I) when R^1 is cycloalkyl, aryl, or heterocyclyl; Z is CO; m = n = r = 0; p = 1; R^3 is $-(CH_2)_{2-3}NR^{11}R^{12}$; $NR^{11}R^{12}$ together form a pyrrolidine moiety substituted in position 3 with one or two R^{17} groups where the first R^{17} group is OH, C_{1-6}alk-oxy, diC_{1-6}alkylamino, or heterocyclyl, and the second R^{17} group is hydrogen or C_{1-6}alkyl (cf. claims 1, 4, 6). In addition, the document discloses specific examples within the overlapping range (cf. examples 162, 163; page 99). Present claims 1 and 3-8 lack thus novelty in view of D2 for the whole overlapping range.

D3 relates to aryloxypiperidines as histamine-3 receptor ligands, the corresponding pharmaceutical composition, and corresponding therapeutic methods. These compounds overlap with the present compounds (I) when R^1 is C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6}alkyl-C_{3-7}cycloalkyl, C_{1-6}alkyl-C_{2-15}heterocyclyl, C_{1-6}alkyl-phenyl; Z is a bond; m = 0-2; p = 1-2 (with regard to R^1, Z, m, and p, see D3, claim 1, where G = $-L_2Q$ or structure (i) with R^{10}); n = 0-1; R^2 is hydrogen or halogen; R^3 is $-(CH_2)_{0-2}$-(1-R^{13}-piperidin-4-yl) according to present structure (i) wherein R^{13} is C_{1-6}alkyl, C_{3-8} cycloalkyl, C_{1-6}alkyl-C_{3-8}cycloalkyl, and C_{1-6}alkyl-phenyl. In addition the document discloses specific examples within the overlapping range (cf. examples 50 (R^1 = CH_3; Z = bond; p = 2; m = 1; n = r = f = 0; R^{13} = i-Pr), 59 (R^1 = CH_3; Z = bond; p = m = 1; n = r = f = 0; R^{13} = i-Pr), 61 (R^1 = benzyl; Z = bond; p = m = 1; n = r = f = 0; R^{13} = i-Pr); 62 (R^1 = phenyl; Z = bond; p = m = 1; n = r = f = 0; R^{13} = i-Pr), 71 (R^1 = R^{13} = i-Pr; Z = bond; p = m = 1; n = r = f = 0)). Present claims 1 and 3-8 lack thus novelty in view of D3 for the whole overlapping range.

D4 relates to selective histamine-3 receptor antagonists, the corresponding pharmaceutical composition, and corresponding therapeutic methods. The compounds of D5 overlap with the present compounds (I) when m = 1 and R^3 is $-(CH_2)_{2-4}NR^{11}R^{12}$ (cf. D5, claim 1). In addition, the document discloses specific examples within the overlapping range (cf. claim 7, compounds 102-105 and 112-115), which are excluded from present claim 1 by means of the first proviso. Nevertheless, the present claims 1 and 3-8 lack novelty in view of D4, because the whole overlapping range is relevant to the question of novelty for the present set of claims rather than only the specific examples.

2.2 **D5** discloses similar histamine-3 receptor ligands as D2. The compounds of D4 overlap with the present compounds (I), and the document discloses specific examples within the overlapping range (cf. examples 162, 163). The document may thus become relevant to the question of novelty in the regional phase.

D6 relates to piperazines as histamine-3 receptor ligands, which overlap with the present compounds (I) when m = 0 (cf. D6, claim 1). Furthermore, the document discloses a specific compound within the overlapping range (cf. example 147; according to present formula (I) wherein R^1 = cyclopentyl; Z is a bond; p = 1; m = n = p = 0; R^3 = $-(CH_2)_2$-N-pyrrolidine). The document may thus become relevant to the question of novelty in the regional phase.

3 Inventive Step and Unity of Invention

The application does not comply with the criteria of inventive step according to Article 33(3) PCT and unity of invention according to Rules 13.1 and 13.2 PCT.

3.1 The documents D1 to D4 disclose already histamine-3 receptor ligands and represent, thus, relevant state of the art. The closest prior art has to be chosen for novel and unitary groups of compounds (I) case by case. However, in view of the severe lack of novelty of present claim 1, the identification of novel and unitary groups of compounds (I) is at present not applicable.

3.2 Nevertheless, with regard to the present specific compounds E1 and E500 the following observations with regard to inventive step would apply. The compound E1 differs e.g. from example 90 of D1 only through R^1-Z as being benzoyl instead of benzyl. Furthermore, the compound E500 is already generally comprised within the compounds of D1 (cf. claim 1, G = L_2Q and L_2 is C_{1-6}alkylene) and differs e.g. from example 91 of D1 in as far as m is 2 instead of 1. D1 may thus considered as closest prior art for the compounds E1 and E500, and the problem to be solved may be seen in the provision (with regard to E1) respectively the selection (with regard to E500) of further histamine-3 receptor ligands. Since the document D1 generally comprises already the present compound E500, and the document D2 teaches already that R^1-Z arylcarbonyl groups (cf. D2, page 120, R^8 = arylcarbonylheterocycle) are compatible with the desired activity, the present claimed compounds E1 (in view of D1 alone) and E500 (in view of D1 in combination with D2) appear to represent merely obvious equivalents of the compounds of D1. In the absence of any common novel structural feature of the claimed compounds which is shown to contribute to any unexpected effect(s) in comparison with the respective closest compounds of the prior art (i.e. present compound E1 compared with example 90 of D1; and present compound E500 compared with example 91 of D1), no inventive step would be acknowledged for the compounds E1 and E500.

3.3 In this context it is also noted that for the requirement of unity to be met the subject-matter should be characterized by a common distinguishing feature over the compounds of the documents D1 to D4. Such common distinguishing feature, however, is at present not evident. Consequently, there is a lack of unity in the sense of Rules 13.1 and 13.2 PCT.

3.4 If the applicant was able to substantiate an unexpected effect for each novel and unitary group of compounds vis-à-vis the respective structurally closest related

compound of the prior art, it is also reminded that the breath of the claims should be such that it represents a reasonable generalization over the examples provided, and such that it is credible that substantially all compounds falling within its scope actually provide a solution to the problem underlying the invention. In this context it is particularly noted that claim 1 contains a plethora of open-ended terms (without being limitative e.g. aryl, heterocyclyl, etc.) that are likely to comprise structures which will not solve any relevant technical problem. For such structures no inventive step would thus be acknowledged.

4 Industrial Applicability

For the assessment of the present claim 7 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5 Deficiencies of the Application under Article 6 PCT

5.1 Present claim 1 relates to an extremely large number of possible compounds (I). The claim contains a plethora of options, variables, open-ended values, possible permutations and, in addition, five provisos respectively disclaimers. Disclaimers may be appropriate to establish novelty of a basically novel class of compounds over some indicated prior art. In the present case, however, provisos respectively disclaimers with regard to the documents D1 to D4 are inappropriate since the claim does not relate to a basically novel class of compounds from which some prior art could be excluded. The claim does, thus, not comply with the requirements of Article 6 PCT.

5.2 Present claim 2 is to be objected under Article 6 and Rule 6.2(a) for referring to the examples of the description. In addition, the phrase "a compound of formula E1-E503" used in claim 2 leaves the reader in doubt if the scope of the claim is limited to the final products of the examples (e.g. the compounds of the formulae E76, E77, etc.) or if the intermediate compounds (e.g. compounds of the formulae E76a, E76b, E76c, etc.) are as well comprised within the scope of the claim, thereby resulting in a lack of clarity of the claim. In addition, the reference to

respectively the inclusion of approximately 500 specific compounds within claim 2 results in a lack of conciseness of the claim and puts undue burden to the reader to establish the scope for which protection is sought.

6 Further Deficiencies of the Application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in **D2** to **D4** is not mentioned in the description, nor are these documents identified therein.